UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NORTH CAROLINA
SOUTHERN DIVISION

AUG 2 2001

aaiPHARMA INC.

Plaintiff,

v.

TOMMY G. THOMPSON, SECRETARY OF HEATH AND HUMAN SERVICES, BERNARD SCHWETZ, DVM, Ph.D., ACTING COMMISSIONER OF UNITED STATES FOOD AND DRUG ADMINISTRATION AND UNITED STATES FOOD AND DRUG ADMINISTRATION,

Defendants.

Civil Action No.: 7-01-CV-152-F

VERIFIED COMPLAINT

A. The Parties

1. Plaintiff aaiPharma Inc. ("aaiPharma") is a Delaware corporation with its principal place of business in Wilmington, North Carolina.

2. Defendant Tommy G. Thompson (the "Secretary") is the Secretary of Health and Human Services, and is sued in his official capacity.

3. Defendant Bernard Schwetz, DVM, PhD, (the "Commissioner") is the Acting Commissioner of Food and Drugs, and is sued in his official capacity.

4. The Secretary and, reporting to him, the Commissioner, are charged with administering the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-397 (the "FDCA"). In 1984, the FDCA was modified by the Drug Price Competition and Patent Term Restoration Act (the "Hatch-Waxman Act"), which consisted of a series of provisions

designed to balance the objectives of making generic drugs available to consumers while at the same time

protecting patent holders whose rights might be infringed by the generic drugs, beyond the protections afforded by the patent laws.

5. Defendant United States Food and Drug Administration ("FDA") is a federal agency charged with enforcing the FDCA Act, including the Hatch-Waxman Act. The FDA is an agency within the Department of Health and Human Services.

B. Jurisdiction and Venue

6. This Court has jurisdiction over this action under 28 U.S.C. § 1331 and 5 U.S.C. § 703.

7. Venue in this District is proper under 28 U.S.C. § 1391.

C. The " Listing" Requirements Under the Hatch-Waxman Act

8. Under the FDCA Act, all prescription drugs must receive FDA approval before they can be marketed. A drug manufacturer wishing to market a new drug containing an active ingredient not previously approved must complete and submit to the FDA a New Drug Application ("NDA") to obtain approval. Pursuant to the Hatch-Waxman Act and implementing regulations, an NDA must include, among other things, the identification of the number and expiration date of "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1).

9. Applicants must also amend NDAs to include such information about any patents required to be listed that issue while the NDA is under review. 21 U.S.C. § 355(b)(1). Upon

approval of an NDA, the FDA must publish and list the patent information identified in paragraph 8 above and in this paragraph. In addition, if a patent required to be listed issues after approval of an NDA, the holder of the approved NDA must inform the FDA within thirty days after issuance of the patent of the same information required in new or pending NDAs. 21 U.S.C. § 355(c)(2). However, the FDA must publish such patent information upon submission. Id.

10. The FDA, in turn, is required to publish information on all patents identified by an applicant in an NDA or a pending NDA, or submitted to the FDA by the application holder after approval of an NDA. 21 U.S.C. §§ 355(b)(1), (c)(2), (j)(7)(a)(iii); 21 C.F.R. § 314.53(e). The FDA publishes this information in a publication officially entitled Approved Drug Products with Therapeutic Equivalence, commonly called the "Orange Book." Significantly, the FDA only publishes patents actually identified by the NDA holder. The FDA will notify the NDA holder and provide it with an opportunity to amend its patent information in the event a party other than the NDA holder advises the FDA that its patent is required to be listed. However, under its regulations and practice, the FDA will not undertake an independent evaluation of the non-NDA holder's claim that its patent should be listed, and will not either require the NDA holder to identify a patent for listing or publish the patent information in the Orange Book. 21 C.F.R. § 314.53(f); *Abbreviated New Drug Application Regulations, Patent Exclusivity Provisions,* 59 Fed. Reg. 50338, 50343 (Oct. 3, 1994). Thus, the FDA's regulations and practice effectively confer on the NDA holder – a private party motivated by economic self-interest - unreviewable discretion to determine whether to identify patents to the FDA for listing, notwithstanding the patent's eligibility for listing under the FDCA Act's criteria, even in situations where the NDA holder is neither the

patent holder nor a licensee of the patent holder but the patent clearly meets statutory listing requirements.

D. The Generic Drug Approval Process and the Protections Afforded to Patent Holders by the "Listing Requirements"

1. Under the Hatch-Waxman Act, instead of preparing an NDA, the proponent of a generic drug can submit an Abbreviated New Drug Application ("ANDA"). As with an NDA, the ANDA must be approved by the FDA before the generic drug can be marketed. However, unlike an NDA holder who bears the burden of proving to the FDA that a new drug product is safe and effective, a generic manufacturer under an ANDA bears the considerably lesser burden of showing that its product has the same active ingredient, labeling requirements, dosage form, bioequivalence and other characteristics of the NDA holder's approved drug. 21 U.S.C. § 355(j)(2).

2. However, to clarify patent infringement issues, the ANDA applicant must certify to the FDA that the generic version will not interfere with any patents listed in the Orange Book. Specifically, the generic manufacturer must certify to one of the following "with respect to each patent" that claims the drug or the same use for the drug for which the generic seeks approval: (I) that such patent information has not been filed in the Orange Book; (II) that such patent has expired; (III) the date on which such patent will expire; or (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. 21 U.S.C. § 355(j)(2)(vii)(I-IV).

3. When an ANDA applicant submits a paragraph IV certification as referenced in paragraph 12 above, the applicant must notify both the patent holder and the NDA holder and provide a detailed statement of the basis for the ANDA applicant's opinion that the patent is

invalid and/or will not be infringed. 21 U.S.C. § 355(j)(2)(B)(i)-(ii). The patent holder then has 45 days in which to initiate a lawsuit against the ANDA applicant for patent infringement. Critically, filing of a suit by the patent holder delays approval of the ANDA for a thirty-month period, unless a court's decision or order results in a different period. 21 U.S.C. § 355(j)(5)(B)(iii). Thus, the "listing" function, and the publication of patents required to be listed in the Orange Book, provides critical protection for patent holders in addition to the protections of the patent laws, irrespective of whether or not they are NDA holders.

E. aaiPharma's Patent and Lilly's Refusal to List

4. On July 10, 2001, U.S. Patent No. 6,258,853 ("the '853 patent") was duly issued to aaiPharma by the United States Patent and Trademark Office ("PTO"), the federal agency responsible for examining patents. A copy of the '853 patent is attached as Exhibit 1. The '853 patent describes and claims pharmaceutical formulations comprising the Form A component of fluoxetine hydrochloride at specified purity levels, and methods of using these formulations. Fluoxetine hydrochloride, a member of the class of antidepressants known as Selective Serotonin Reuptake Inhibitors ("SSRIs"), is the active pharmaceutical ingredient in Lilly's Prozac® drug product. Form A of fluoxetine hydrochloride is a polymorphic variant, or component, of fluoxetine hydrochloride.

5. Lilly is the holder of one or more approved NDAs for fluoxetine hydrochloride, which it markets as Prozac®. In conjunction with Prozac®, the Orange Book presently lists a number of patents assigned to Lilly, including U.S. Patent No. 4,314,081 of relevance here, as that patent effectively has prevented FDA approval of ANDAs for generic fluoxetine

hydrochloride, until its expiration (including a six-month pediatric extension) at midnight on August 2, 2001.

6. aaiPharma's '853 patent is required to be listed in the Orange Book for fluoxetine hydrochloride, because it claims a polymorphic component (Form A) of fluoxetine hydrochloride, the drug for which Lilly submitted the application. aaiPharma has performed testing on Lilly's Prozac® which demonstrates that fluoxetine hydrochloride as the active ingredient in Lilly's Prozac® includes Form A as a component. A claim of patent infringement could reasonably be asserted if a person, such as a generic drug manufacturer not licensed by aaiPharma, engaged in the manufacture, use, or sale of the drug which satisfied the claims of the '853 patent. These are the statutory tests for Orange Book listing by the agency under 21 U.S.C. § 355(b)(1). Under 21 U.S.C. § 355(c)(2), they apply equally to any Lilly approved NDA for fluoxetine hydrochloride.

7. aaiPharma has sent letters of inquiry to each generic drug manufacturer presently in line for FDA ANDA approval to manufacture and sell generic forms of fluoxetine hydrochloride, seeking information to allow aaiPharma to evaluate whether these manufacturers would infringe the '853 patent. Copies of these letters are attached as Exhibit 2. To date, aaiPharma has not received any substantive evidence of non-infringement from these generic manufacturers. aaiPharma could reasonably assert a claim of patent infringement against any of these generic manufacturers who, without authorization from aaiPharma, manufactured, used or sold a generic version of Prozac® which satisfied the limitations set forth in the any of the claims of aaiPharma's '853 patent.

8. aaiPharma has requested Lilly to amend its NDAs for Prozac® to identify the '853 patent for listing. However, Lilly has refused to do so.

9. Under its regulations and practice, although the FDCA, as amended by the Hatch-Waxman Act, requires Lilly to amend its NDA for Prozac® so that the '853 patent is listed in the Orange Book, the FDA will not take any action against Lilly or publish information regarding the '853 patent in the Orange Book. On July 18, 2001, aaiPharma sent a letter to the FDA requesting that it vindicate its patent rights under the Hatch-Waxman Act (copy attached as Ex. 3), but the FDA's only response was to send a letter to Lilly, the NDA holder, advising Lilly of aaiPharma's concerns and confirming that the FDA would not list aaiPharma's patent unless Lilly identified it in its NDA (copy attached as Ex. 4).

10. As noted previously, Lilly's claim for exclusivity under the patent laws for Prozac® is scheduled to expire at midnight on August 2, 2001, and a number of companies have submitted ANDAs for generic versions of Prozac®. Because the '853 patent was not identified by Lilly in its NDA, and because the FDA will not publish and list the patent in the Orange Book without such identification by Lilly, these companies will be permitted to avoid submitting paragraph IV certifications claiming invalidity or non-infringement of the '853 patent, and thereby to avoid the applicable Hatch-Waxman provisions designed to protect aaiPharma's patent rights.

11. Unless the relief requested herein is granted, the ANDAs for the generic versions of Prozac® will be approved after midnight August 2, 2001, and aaiPharma will forever lose its statutory remedies under the Hatch-Waxman Act for protecting its patent, including a thirty month stay of the approval of ANDAs, which it would be entitled to invoke if aaiPharma's '853 patent were listed.

COUNT I

(Unlawful Delegation of Authority in Violation of Administrative Procedure Act)

12. aaiPharma restates and incorporates by reference the allegations in paragraphs 1-21 above.

13. The FDA's regulations, implementation thereof, practice, and refusal to take action to require Lilly to identify the '853 patent in its NDA for Prozac®, unlawfully delegate to a private party the FDA's statutory duty to require compliance with the listing requirements under the Hatch-Waxman Act. The FDA's regulation and conduct are arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law (5 U.S.C. § 706(2)(A)); in excess of statutory jurisdiction, authority, or limitations, or short of statutory right (5 U.S.C. § 706(2)(c)); and without observance of procedure required by law (5 U.S.C. § 706(2)(D)). This Court should hold the FDA's regulations and conduct unlawful (5 U.S.C. § 706(2)), and order appropriate relief, including compelling the FDA to take action unlawfully withheld (5 U.S.C. § 706(1)).

WHEREFORE, aaiPharma prays that this Court:

1. Enter a temporary restraining order and a preliminary injunction enjoining the Secretary, the Commissioner, and the FDA from approving any ANDA for a generic version of Prozac®, pending a determination on whether the '853 patent is required to be identified in Lilly's NDA for Prozac® and listed in the Orange Book; and

2. Upon such determination, order the Secretary, the Commissioner, and the FDA to take all necessary action to require Lilly to amend its NDA for Prozac® to identify the '853 patent and its expiration date, and upon such identification, forthwith publish the required patent information in the Orange Book, and continue the temporary restraining order and preliminary injunction until such time as the '853 Patent is identified and listed in Lilly's NDA for Prozac® and listed in the Orange Book;

3. Enter a final judgment in favor of aaiPharma; and

4. Grant such further relief as is just and proper.

Respectfully submitted this 2nd day of August 2001.

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STATE OF NORTH CAROLINA

COUNTY OF NEW HANOVER

VERIFICATION

Dr. Frederick D. Sancilio, being first duly sworn, deposes and says that he is the Chairman of the Board and Chief Executive Officer of aaiPharma, Inc., the plaintiff in the foregoing action, and that he has read the foregoing Complaint and knows the contents thereof, based upon information known to him personally, information set forth in public sources and information provided to him by persons with personal knowledge, and the same is true of his own knowledge, except as to those matters therein stated upon information and belief, and as to those matters he believes them to be true.

Subscribe and Sworn to
before me this 1st day
of August, 2001.

Notary Public

My commission Expires: April 4, 2006

[Notarial Seal]

US006258853B1

(12) **United States Patent**
Stowell et al.

(10) **Patent No.: US 6,258,853 B1**
(45) **Date of Patent: Jul. 10, 2001**

(54) **FORM A OF FLUOXETINE HYDROCHLORIDE**

(76) Inventors: **Grayson Walker Stowell**, 710 Darwin Dr., Wilmington, NC (US) 28405; **Robert R. Whittle**, 5006 Pine Needles Dr., Wilmington, NC (US) 28403

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/772,992**

(22) Filed: **Jan. 31, 2001**

(51) **Int. Cl.**[7] **A61K 31/135**
(52) **U.S. Cl.** **514/651**
(58) **Field of Search** 514/651

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,296,126	10/1981	Nedelac et al.	424/316
4,314,081	2/1982	Molloy et al.	564/347
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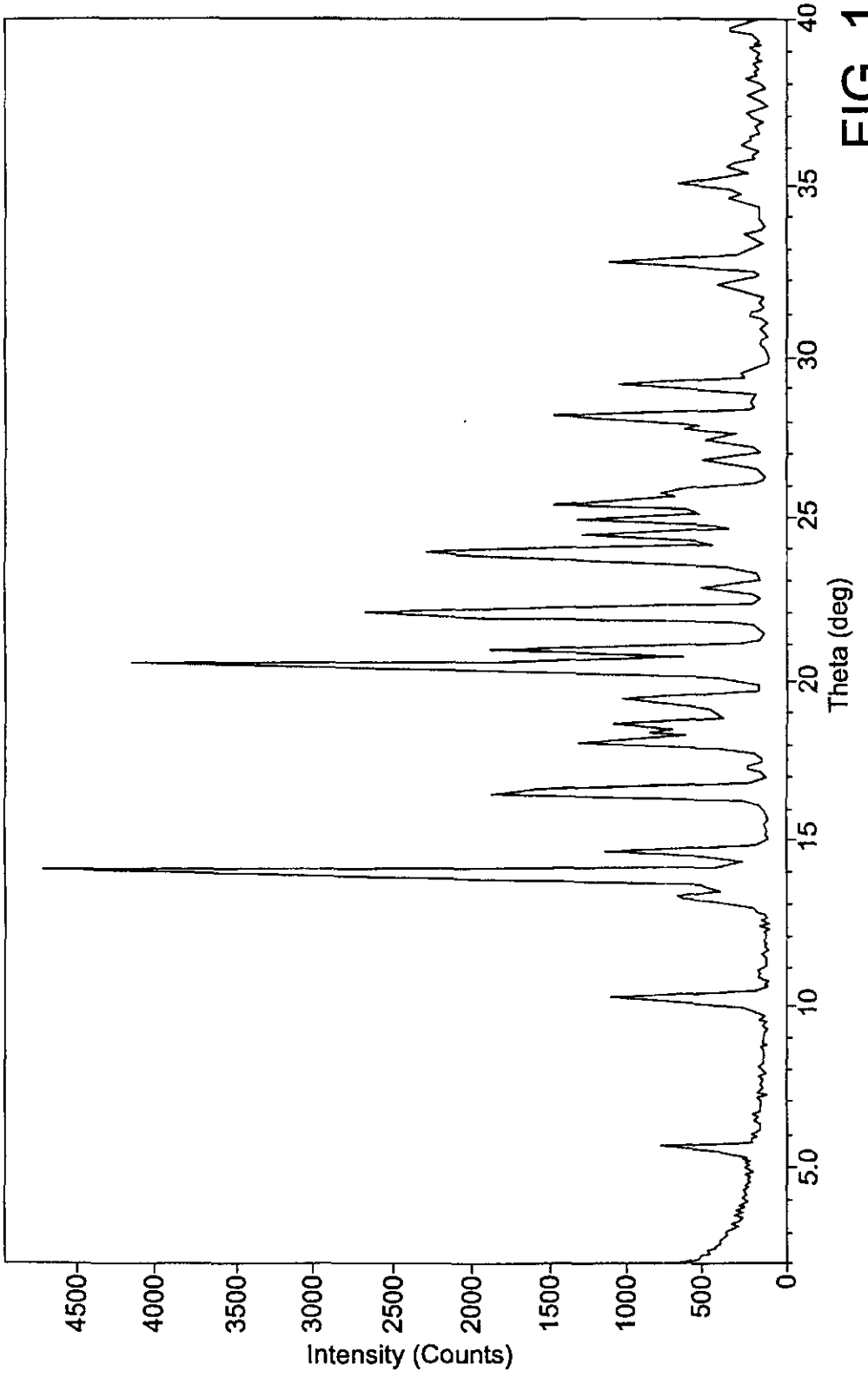
0 391 070 B1	1/1994	(EP)	C07C/217/62
0 529 842 B1	4/1996	(EP)	C07C/213/06
2060618	5/1981	(GB)	C07C/93/14
WO 94/00416	1/1994	(WO)	C07C/217/48
WO 98/11054	3/1998	(WO)	C07C/213/08
WO 99/49857	10/1999	(WO)	A61K/31/135

Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Myers Bigel Sibley & Sajovec, P.A.; Steven A. Fontana, Esq.

(57) **ABSTRACT**

The present invention relates to novel pharmaceutical formulations and methods of using Form A of fluoxetine hydrochloride.

20 Claims, 11 Drawing Sheets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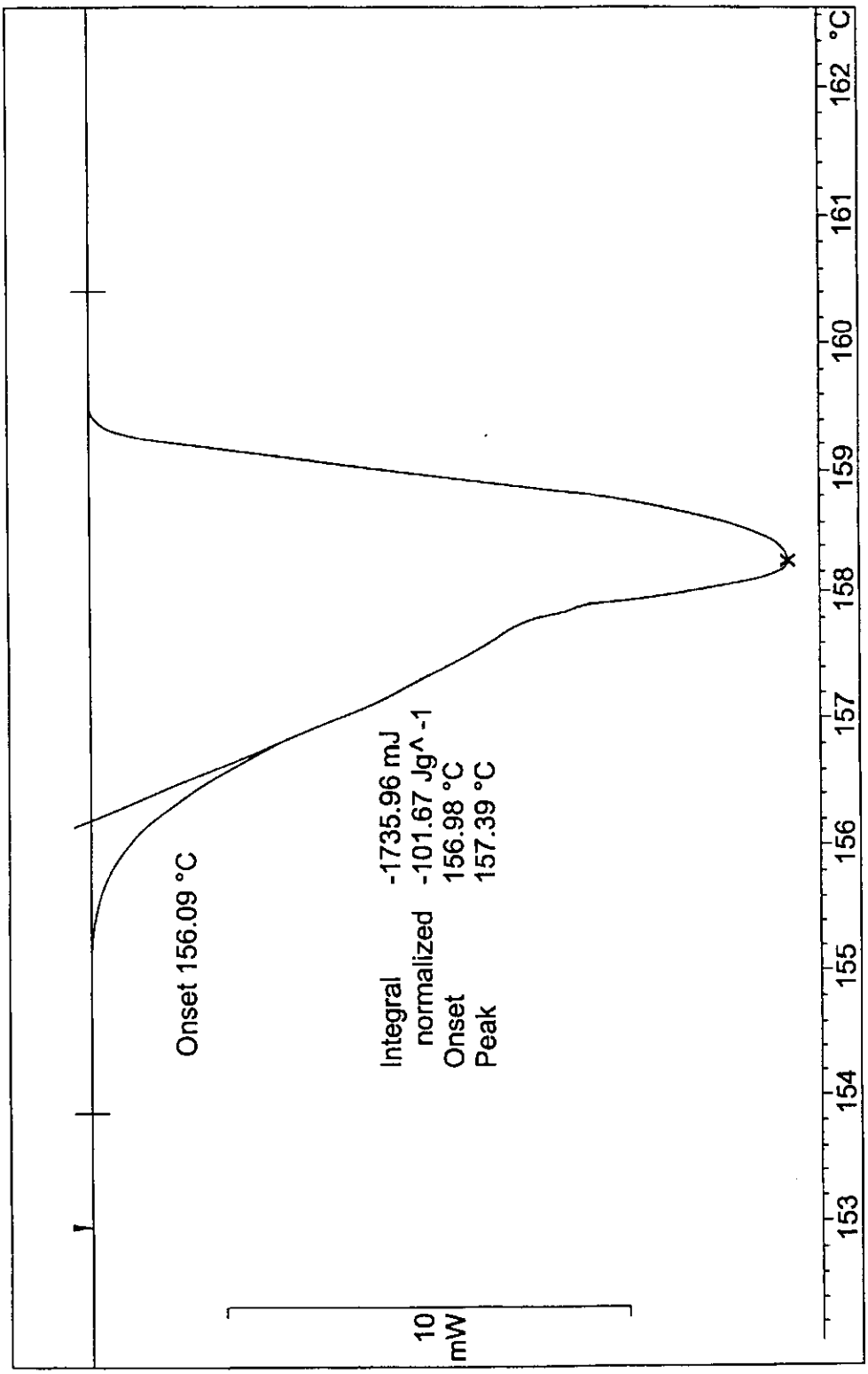
Theta (deg)

FIG. 1.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158
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162 °C

FIG. 2.

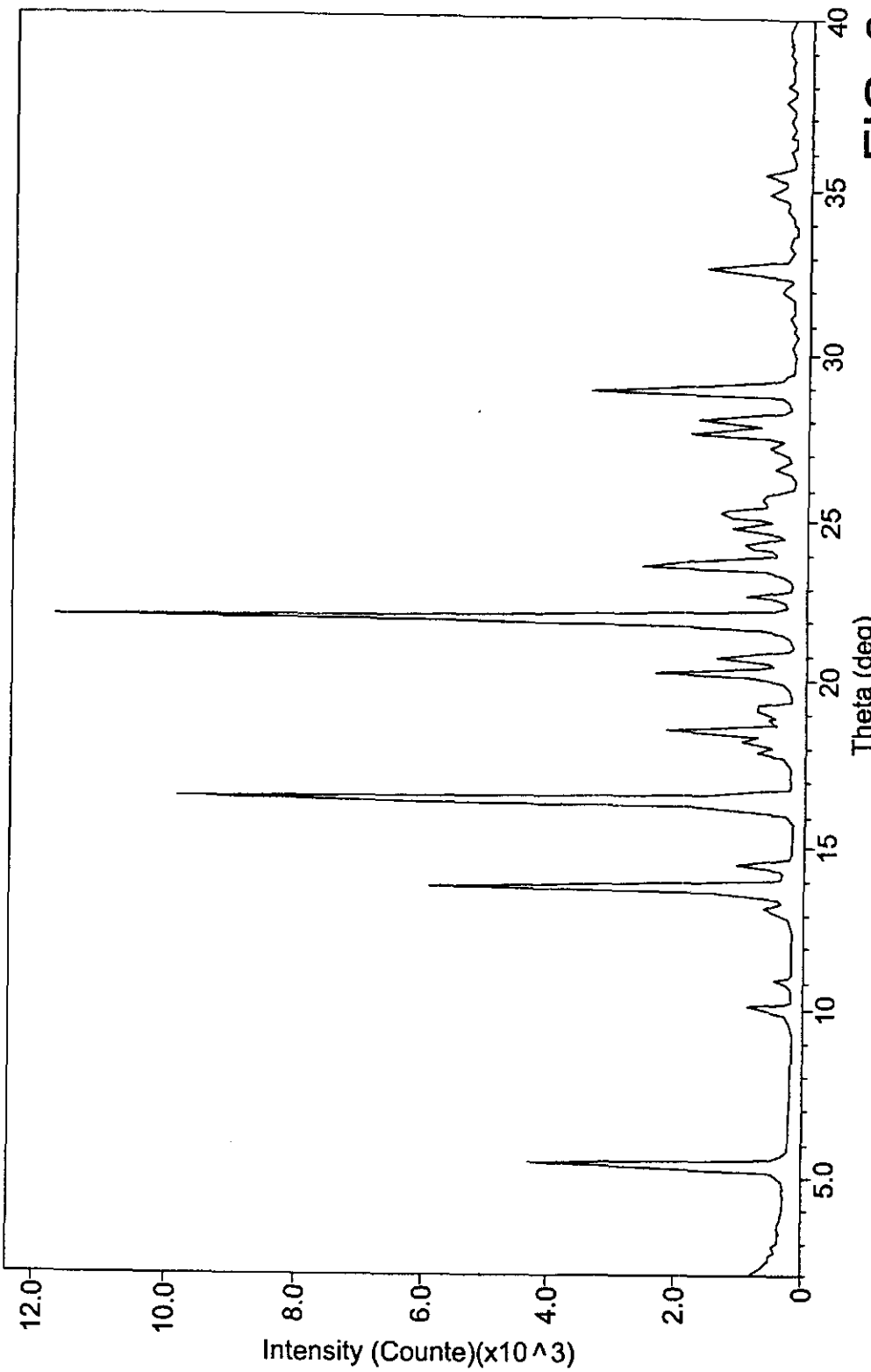
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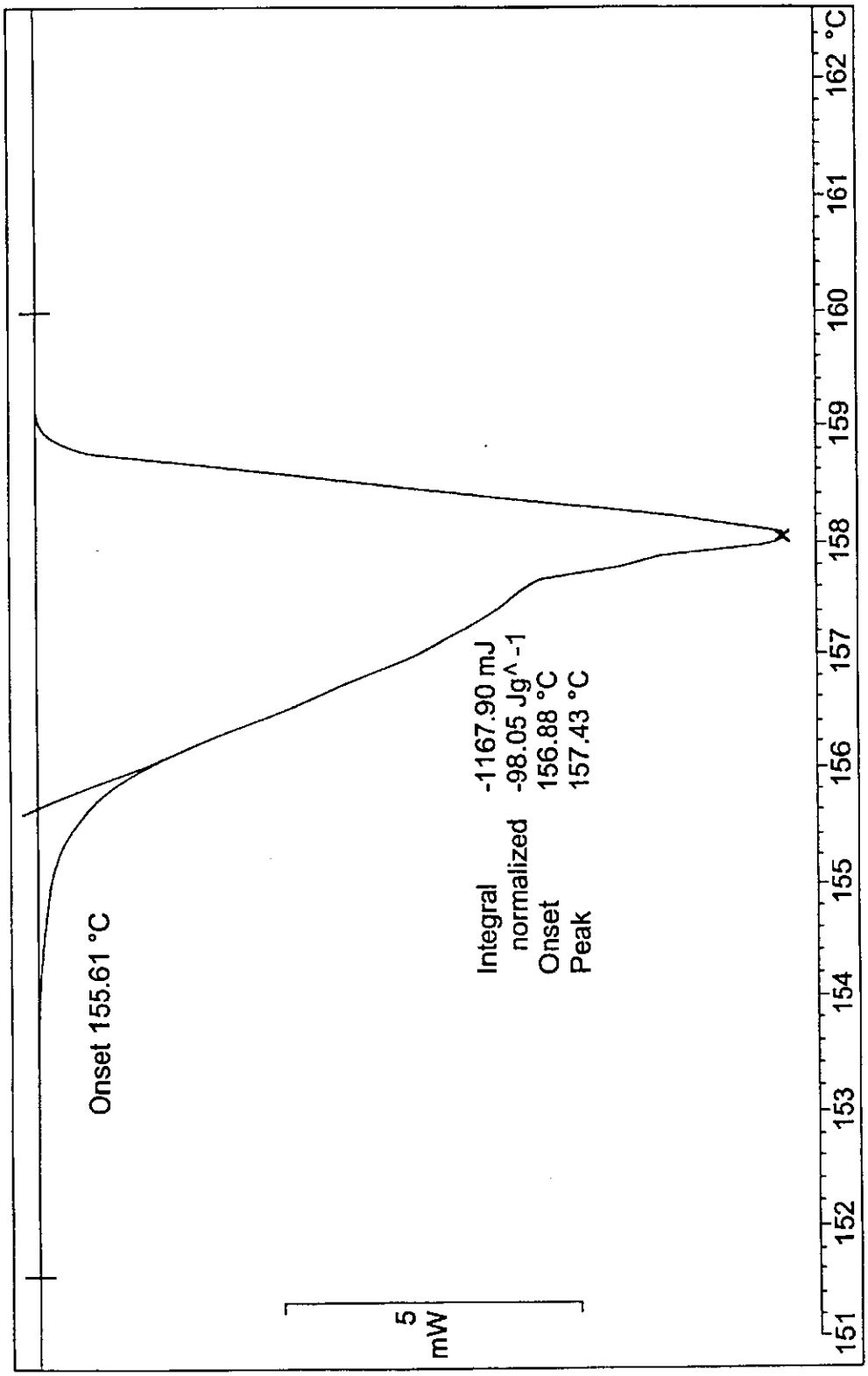
FIG. 3.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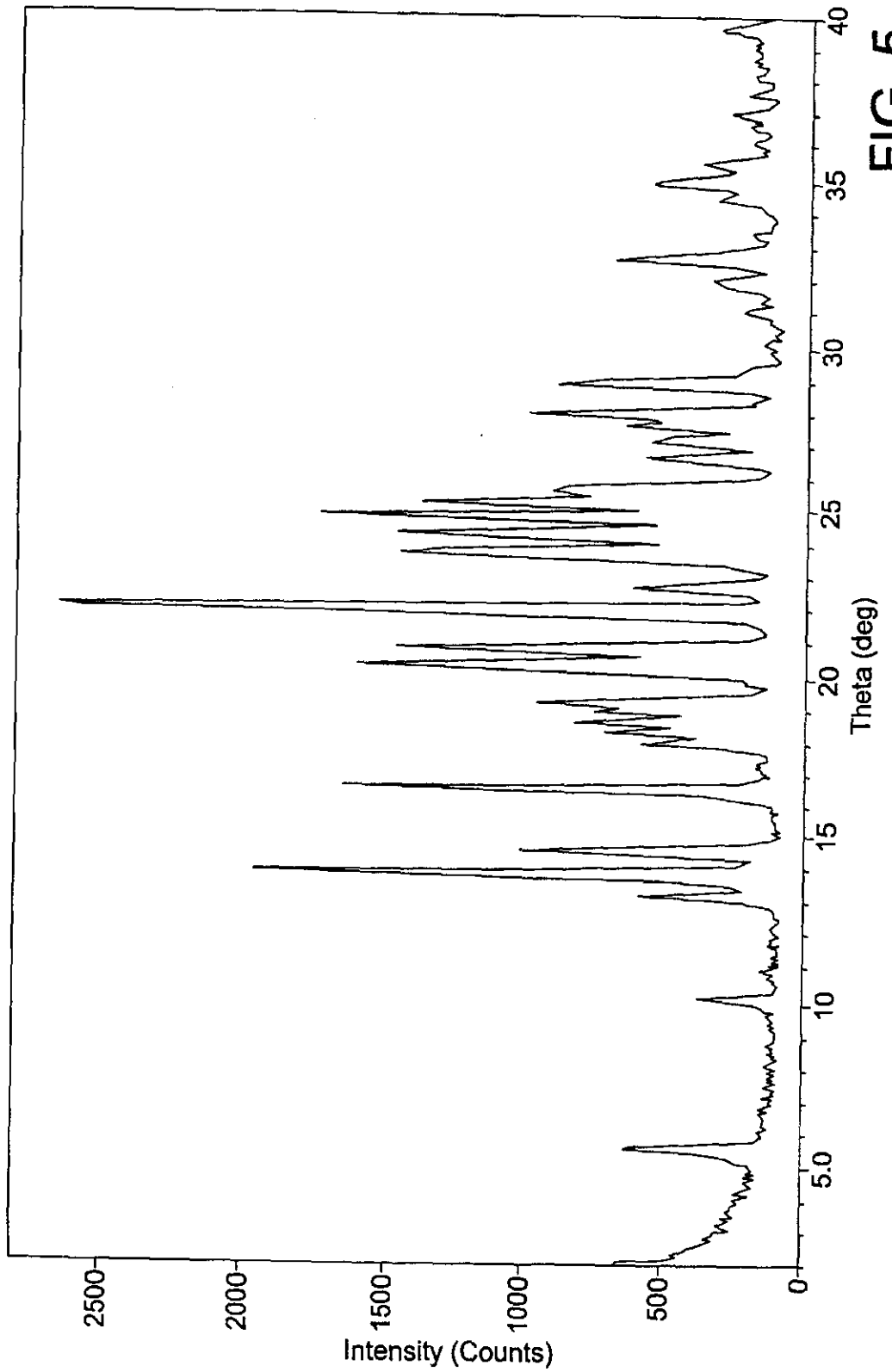
161
162 °C

FIG. 4.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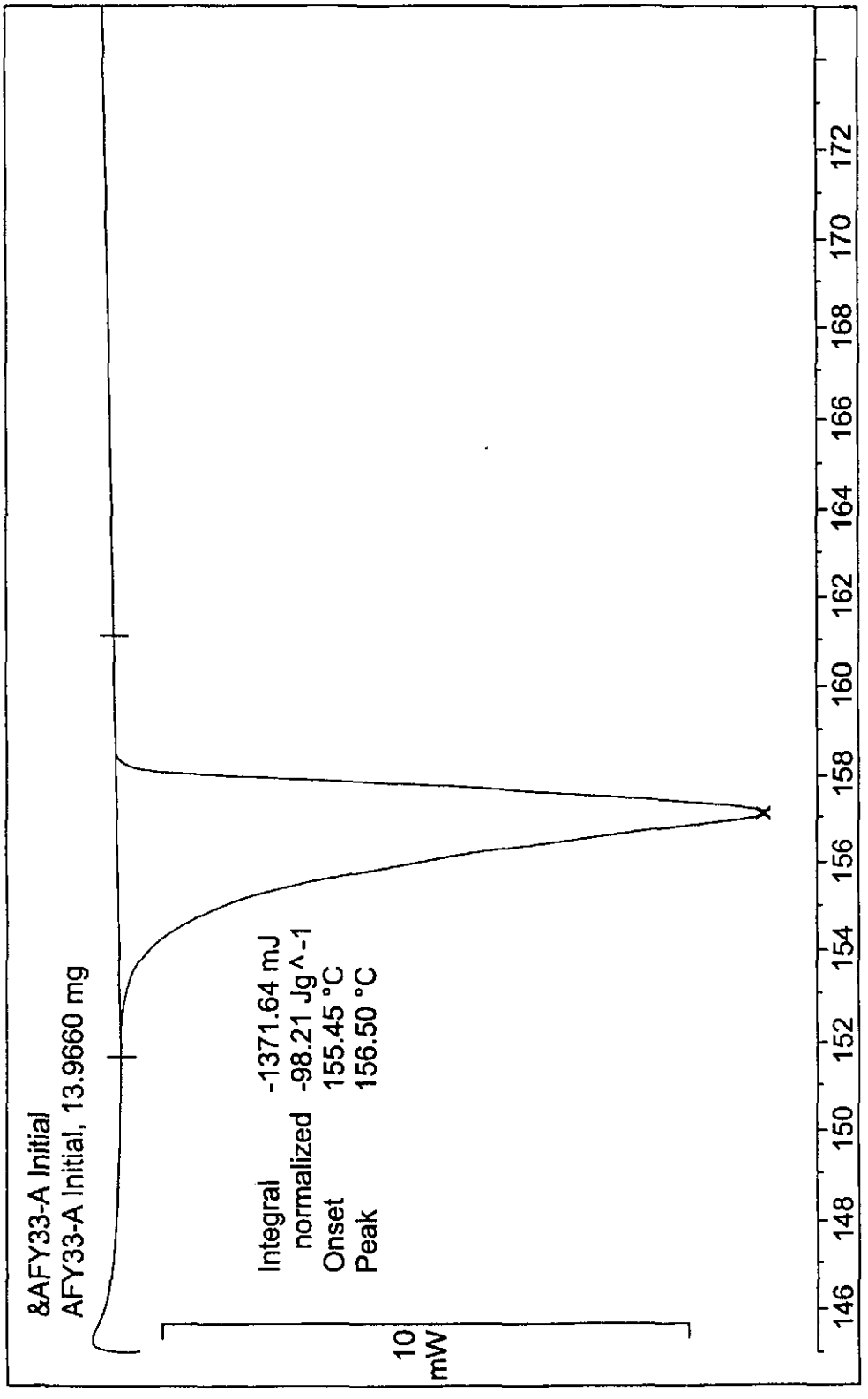
Theta (deg)

FIG. 5.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normalized -98.21 Jg^-1
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172

FIG. 6.

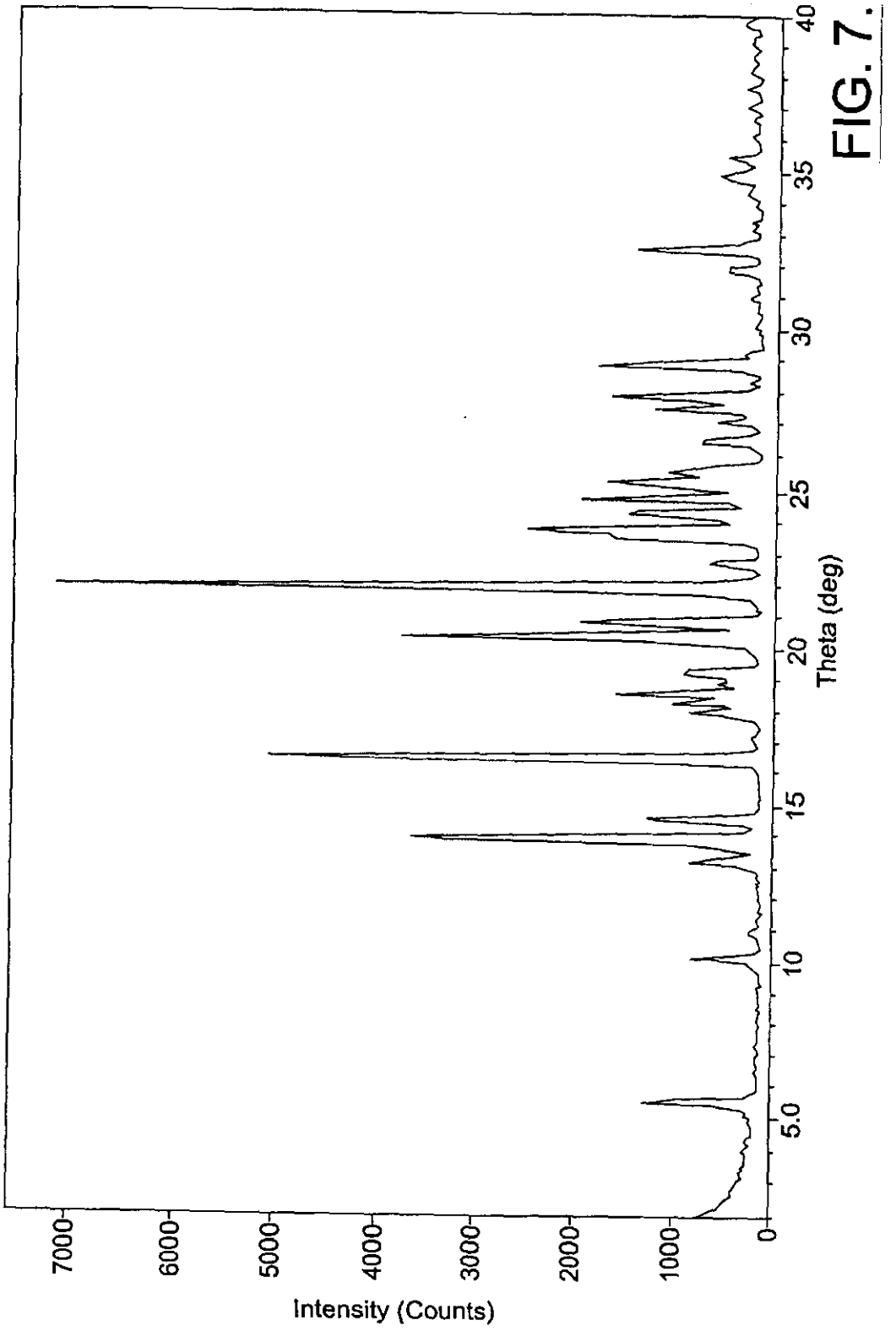
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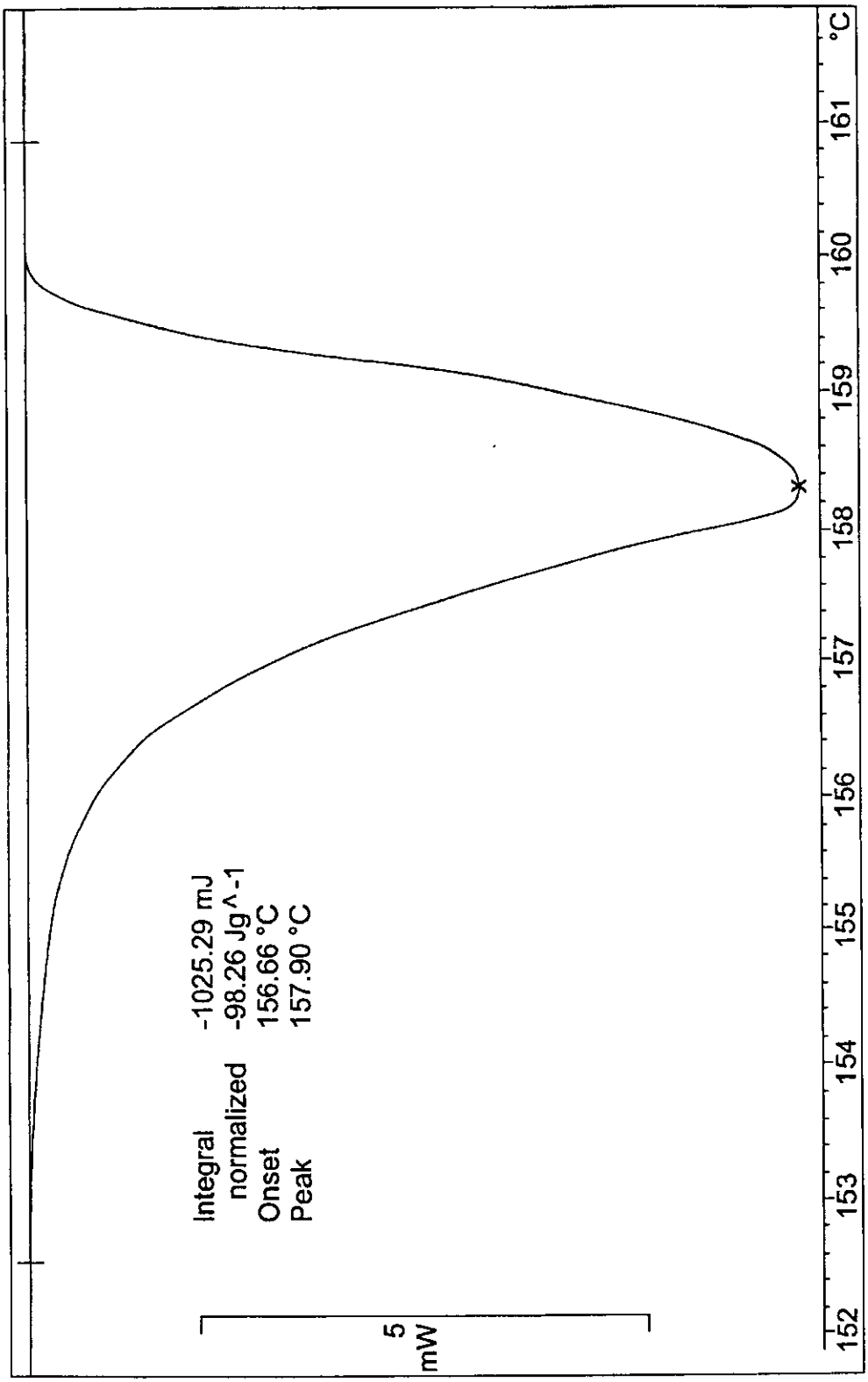
FIG. 7.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°C

FIG. 8.

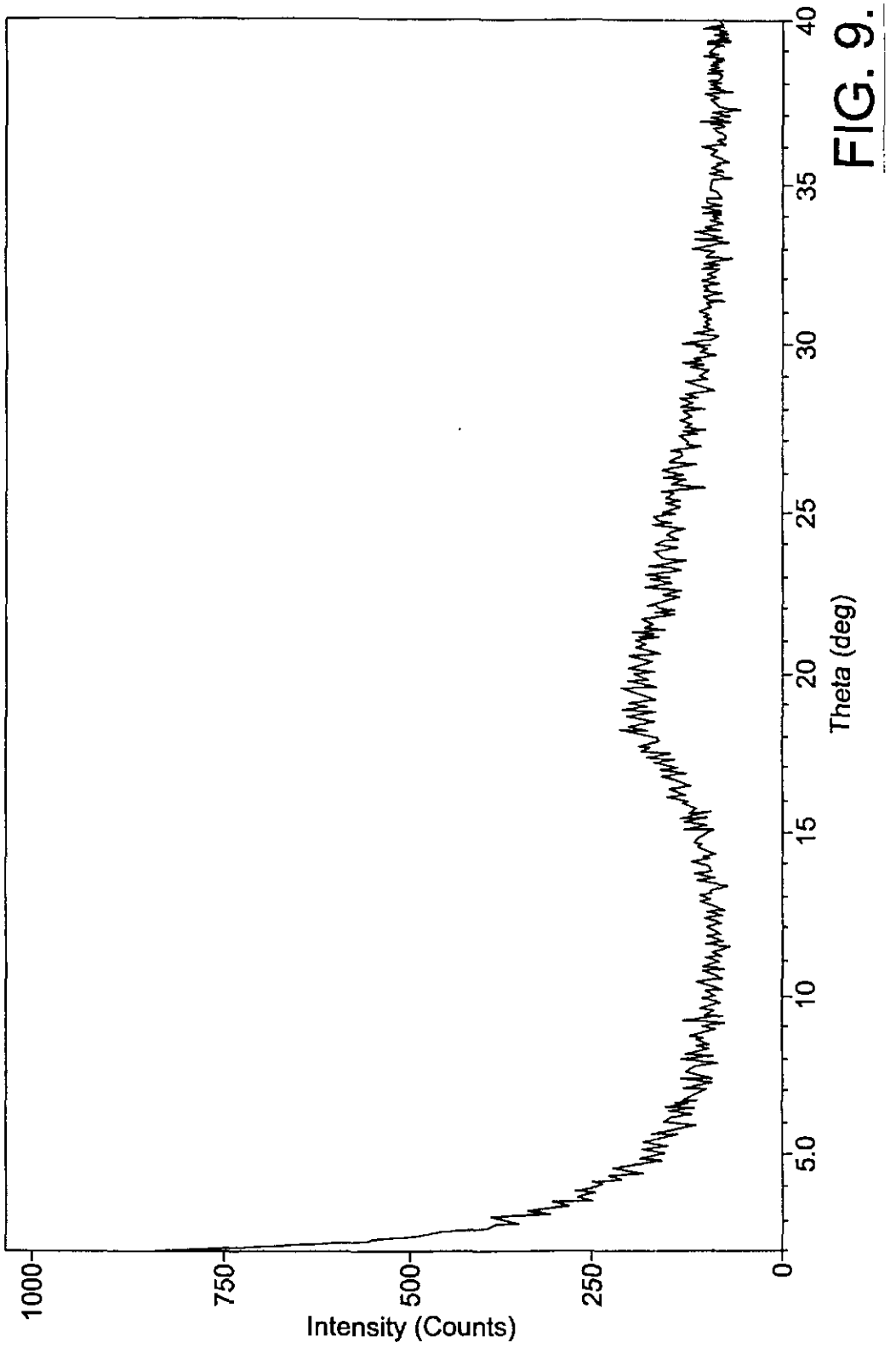
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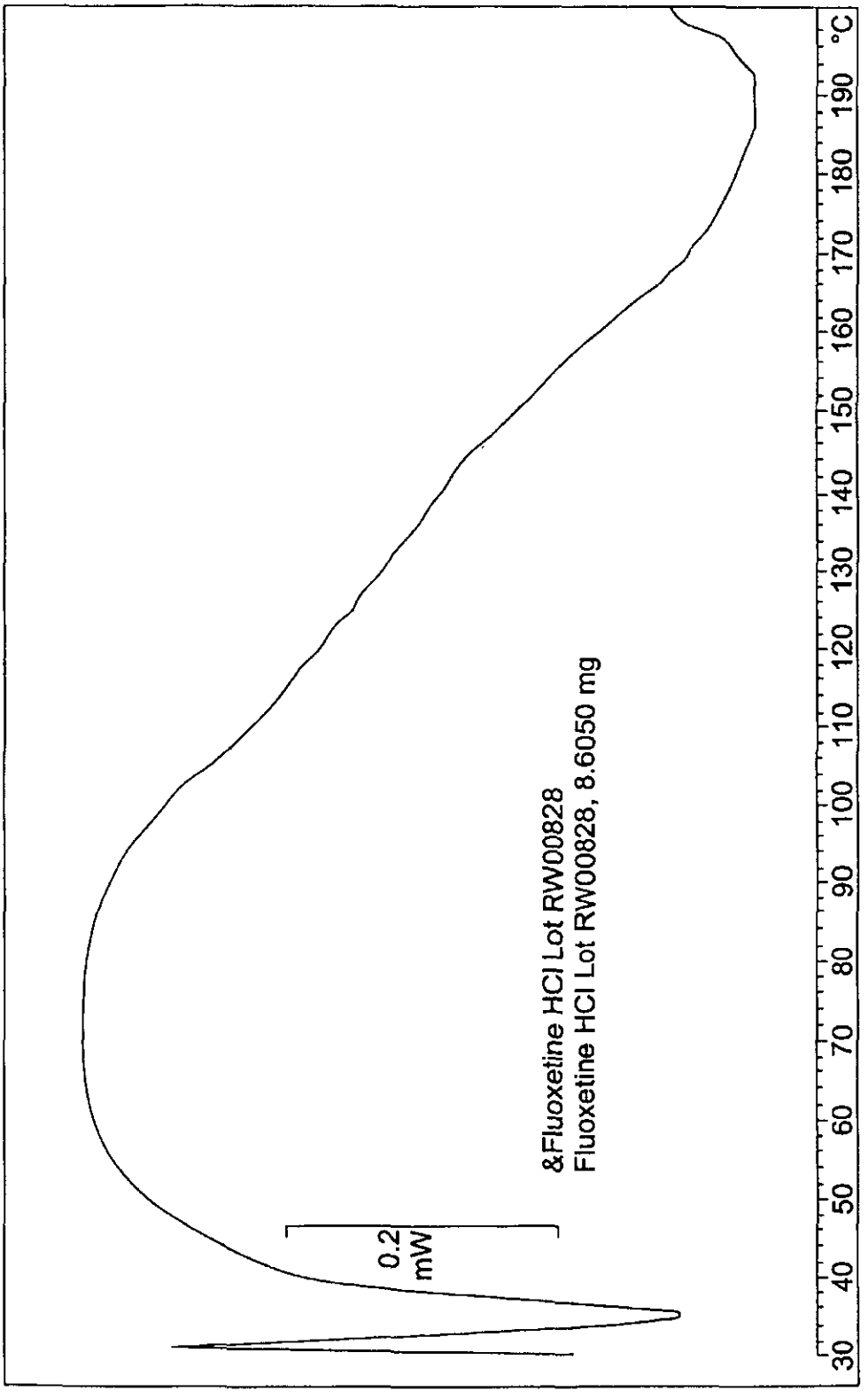
FIG. 9.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30
40
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70
80
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100
110
120
130
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mW
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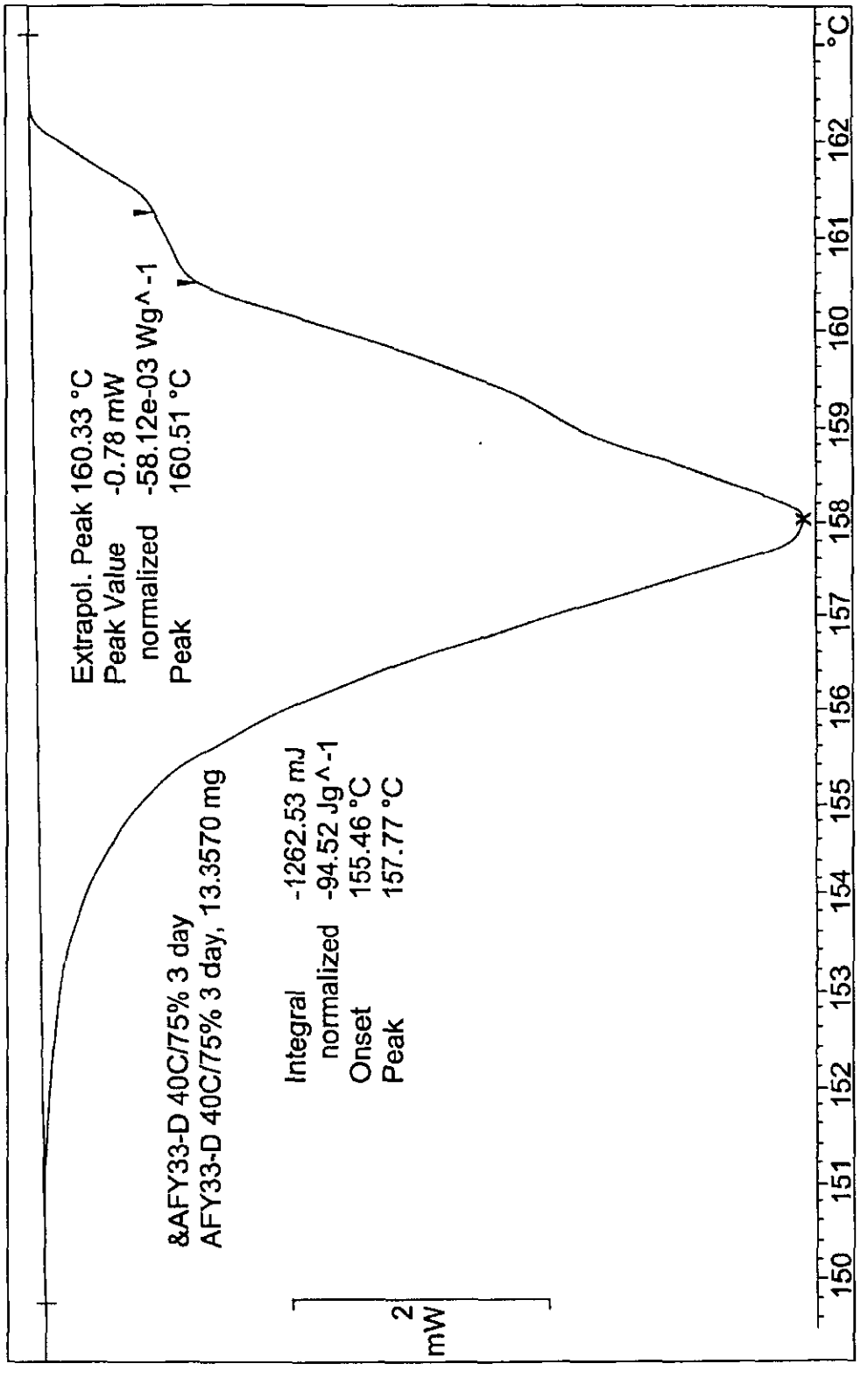
FIG. 10.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normalized -58.12e-03 Wg^-1
Peak 160.51 °C
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AFY33-D 40C/75% 3 day, 13.3570 mg
Integral -1262.53 mJ
normalized -94.52 Jg^-1
Onset 155.46 °C
Peak 157.77 °C
2 mW
150 151 152 153 154 155 156 157 158 159 160 161 162 °C

FIG. 11.

FORM A OF FLUOXETINE HYDROCHLORIDE

The present invention is generally concerned with a novel polymorphic form of fluoxetine hydrochloride, (±)-N-methyl-3-phenyl-2-[α,α,α- trifluoro-p-tolyl) oxy] propylamine hydrochloride, which is marketed by Dista Products and Eli Lilly and Company (the "Innovator"), Indianapolis, Ind., under the trade name Prozac®. The present invention is further concerned with the preparation and use of the polymorphic form of fluoxetine hydrochloride now designated Form A ("Form A").

Polymorphic forms of the same drug substance (also known as the active pharmaceutical ingredient or "API"), as administered by itself or formulated as a drug product (also known as the final or finished dosage form) are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, fractability, and compressibility of drug substances and the safety and efficacy of drug products, (see, e.g. *Knapman, K. Modern Drug Discoveries*, March, 2000: 53). So critical are the potential effects of different polymorphic forms in a single drug substance on the safety and efficacy of the respective drug product(s) that the United States Food and Drug Administration (the "FDA") requires each drug substance manufacturer, in the least, to control its synthetic processes such that the percentages of the various respective polymorphic forms, when present, must be consistent among batches and within the drug substance/product's specification as approved by the FDA.

Left uncontrolled in synthetic processes, the percentage of a given polymorph outside of an FDA approved specification would render the adulterated batches unfit for commercial sale. Accordingly, the FDA requires full characterization of each drug substance used in each drug product marketed in the United States, including the identification and control of polymorphic forms. The FDA further requires robust synthetic process specifications and controls which consistently produce the respective drug substance and drug product.

Unfortunately, the detection of various polymorphic forms of a single drug substance is not always readily discernable by pharmaceutical chemists. Such a drug substance would not be manufactured with appropriate controls, potentially leaving the attendant safety and efficacy risks unaddressed.

It has been discovered that fluoxetine hydrochloride drug substance, generally used to prepare Prozac® and potential generic drugs thereto (fluoxetine hydrochloride API), has not been fully or completely characterized. It has been unexpectedly discovered that such fluoxetine hydrochloride API drug substance comprises at least three crystalline forms, which occur at varying and uncontrolled ratios from batch to batch. These three identified polymorphs have been designated Form A, Form B, and Form C, correlated to the relative proportion of each polymorph in fluoxetine hydrochloride, from greatest to least.

It has further been discovered that Form A can be prepared in pure or essentially pure polymorphic form in robust, controllable, synthetic processes.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. 1 shows an X-ray powder diffraction (XRD) pattern for fluoxetine hydrochloride API (Lot 1).

FIG. 2 shows the corresponding differential scanning calorimeter (DSC) thermogram for the fluoxetine hydrochloride API sample represented in the XRD pattern shown in FIG. 1.

FIG. 3 shows another XRD pattern for fluoxetine hydrochloride API (Lot 2).

FIG. 4 shows the DSC thermogram for the fluoxetine hydrochloride API sample represented in the XRD pattern shown in FIG. 3.

FIG. 5 shows an XRD pattern for pure Form A of fluoxetine hydrochloride prepared via the compression method of preparation taught herein.

FIG. 6 shows the DSC thermogram for the Form A sample represented in the XRD pattern shown in FIG. 5.

FIG. 7 shows an XRD pattern for pure Form A of fluoxetine hydrochloride prepared via the slurry method of preparation taught herein.

FIG. 8 shows the DSC thermogram for the Form A sample represented in the XRD pattern shown in FIG. 7.

FIG. 9 shows an initial XRD pattern for amorphous fluoxetine hydrochloride prepared via the method taught herein.

FIG. 10 shows the initial DSC thermogram from the amorphous fluoxetine hydrochloride sample represented in the XRD pattern shown in FIG. 9.

FIG. 11 shows a DSC thermogram for Forms A, D, and E, which formed within three days after pure Form A of fluoxetine hydrochloride was prepared via the recrystallization method taught herein when stored at 40° C. and 75% relative humidity.

DETAILED DESCRIPTION OF THE INVENTION

The existence of the various polymorphic forms of fluoxetine hydrochloride can not be discerned from the crystallographic literature. More particularly, literature (Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T. *J. Med. Chem.* (1988), 31, 185) reports the crystal structure of fluoxetine hydrochloride API performed at Lilly Research Laboratories. This article details the crystal structure and parameters associated with the structural analysis. The structure was solved in a non-standard setting (Pcab) of the standard Space Group Pbca (#61) and refined to a final R of 0.074. We have independently also solved the identical structure using the standard setting of Pbca (#61) and have refined the structure to a final R of 0.038. Generation of a simulated powder pattern from the crystallographic data reveals a pattern similar to the pattern that Lilly submitted to the International Center for Diffraction Data (ICDD) for inclusion as file #36-1895 in its powder diffraction database [Orthorhombic, Pcab, 10.457x 10.387x32.345 Å]. However, the ICDD database also lists a second file (#44-1517) for fluoxetine hydrochloride. This file was taken from diffraction data presented by Risley, D.; Bopp, R. *Anal. Profiles Drug Subst.*, (1990), 19, and indexed by the editor of ICDD [Orthorhombic, 10.448x14.797x 32.329 Å]. When actual X-ray powder diffraction was performed using a zero background sample mount on the same crystalline material used for single crystal analysis, the measured pattern was found to match ICDD file #44-1517. The crystals were platelets and zero background sample mounts can induce preferred orientations to a powder pattern. To test this, the respective sample was lightly ground to a more uniform size and shape and front packed in an aluminum sample well to produce a random distribution, and reanalyzed by X-ray powder diffraction. The pattern now matches #36-1895, consistent with the structural analysis indicating that patterns #36-1895 and #44-1517 in the ICDD database are the same crystalline phase and differ only

by severe preferred orientation problems. Closer examination of the two ICDD patterns show they exhibit extremely similar "d" spacings and unit cell constants which differ only in the b-axis length. Indexing of ICDD pattern #36-1895 was based upon single crystal analysis and pattern #44-1517 by indexing from powder diffraction. Indexing (3-D data) from powder diffraction data (2-D data) is considered inconsistent at best, and in this case, appears to have problems. Based upon the axial lengths of 10.457 and 10.387 Å from #36-1895, a special transformation exists. This type of transformation converts the axes to a C-centered cell by using the diagonal of the orthogonal a and b axes, and would generate a cell length of about 14.74 Å for the diagonal (square root of the sum of the squares of the a and b axes) which was assigned to the b-axis. Therefore, the two patterns listed for fluoxetine hydrochloride in the ICDD database are actually the same, differing only in severe preferred orientation. Neither sample even remotely suggests that multiple fluoxetine hydrochloride polymorphs exist. In fact, a combination of analytical tools were required to discover the existence of multiple polymorphic forms of fluoxetine hydrochloride and to confirm that Form A was successfully prepared in pure and essentially pure form.

Using the procedure taught in Example 14 herein, Form A of fluoxetine hydrochloride is characterized by the following single crystallographic parameters:

crystal class	orthorhombic
space group	Pbca (#61)
a(Å)	10.3754 (4)
b(Å)	10.4603 (2)
c(Å)	32.3412 (12)
V(Å^3)	3510.0 (3)
D calc (g/cm^3)	1.31
R, R_w	0.038, 0.038

X-ray powder diffraction is another tool typically available for the characterization of mixtures of polymorphs and individual polymorphs of the same substance. However, visual review of powder patterns for fluoxetine hydrochloride API samples (FIGS. **1** and **3**) are indistinguishable from Form A powder patterns (FIGS. **5** and **7**). When such powder patterns are expressed in terms of "d" spacings and relative intensities, only slight differences among samples are observed (Table 1 below) and are attributable to the sample height packing within the sample holder ("d" spacings) and preferred orientations (relative intensities).

TABLE 1

X-Ray Powder Diffraction Sample							
Lot 1 API[1]		Lot 2 API[2]		Compression[2]		Method Slurry[2]	
d(Å)	I[3]	d(Å)	I[3]	d(Å)	I[3]	d(Å)	I[3]
15.68	w	16.12	m	15.89	w	15.93	w
8.62	w	8.77	w/vw	8.64	w/vw	8.67	w/vw
6.63	w/vw	6.71	vw	6.65	w	6.67	w/vw
6.32	vs	6.39	s	6.33	s/vs	6.35	s
6.04	w	6.10	w/vw	6.04	m	6.06	w
5.36	m/s	5.39	vs	5.36	s	5.37	s/vs
4.91	w	4.94	vw	4.92	w	4.92	w/vw
4.83	w	4.86	w/vw	4.83	w	4.84	w/vw
4.58	w	4.61	vw	4.60	m	4.62	w/vw
4.34	vs	4.37	w	4.35	s	4.35	s
4.24	m	4.27	w	4.25	m/s	4.26	w

TABLE 1-continued

X-Ray Powder Diffraction Sample							
Lot 1 API[1]		Lot 2 API[2]		Compression[2]		Method Slurry[2]	
d(Å)	I[3]	d(Å)	I[3]	d(Å)	I[3]	d(Å)	I[3]
4.02	s	4.04	vs	4.02	vs	4.03	vs
3.89	w/vw	3.92	w/vw	3.90	w	3.90	w/vw
3.72	m/s	3.77	w	3.74	m/s	3.74	w
3.64	w/vw	3.66	vw	3.64	w	3.65	w/vw
3.57	w/vw	3.59	vw	3.58	m	3.58	w/vw
3.50	m	3.53	w	3.51	m	3.51	w
3.46	w	3.48	vw	3.47	m	3.48	w
3.33	w/vw	3.35	vw	3.34	w/vw	3.34	w/vw
3.26	vw	3.28	vw	3.27	vw	3.27	vw
3.17	m	3.19	w	3.18	m	3.18	w
3.07	m/w	3.09	m/w	3.07	m/w	3.08	m/w
2.86	vw	2.88	vw	2.87	vw	2.87	vw
2.79	vw	2.80	vw	2.79	vw	2.79	vw
2.73	w	2.74	w	2.74	w	2.74	w
2.55	w/vw	2.57	vw	2.56	w/vw	2.56	vw
2.42	vw	2.43	vw	2.42	vw	2.42	vw

[1]Typical fluoxetine hydrochloride API
[2]Form A of fluoxetine hydrochloride prepared as taught hereinbelow.
[3]vw = very weak; w = weak; m = moderate; s = strong; and vs = very strong intensities.

Accordingly, x-ray powder diffraction serves as a useful tool for confirming the presence of fluoxetine hydrochloride, but is not a useful tool for differentiating among the various individual or mixtures of polymorphs of fluoxetine hydrochloride. However, when used in combination with differential scanning calorimetry (DSC), x-ray powder diffraction is used to confirm the presence of fluoxetine hydrochloride (see, e.g., Example 15), and DSC is used to confirm the presence of Form A, in pure and essentially pure form, and mixtures of fluoxetine hydrochloride polymorphs.

Using the appropriately precise DSC method set forth in Example 12 herein, wherein the analysis is conducted at a maximum rate of 1° C. per minute, multiple levels of polymorph Forms A, B, and C each are typically present in fluoxetine hydrochloride API (FIGS. **2** and **4**). When such API is prepared via any one of the methods of the present invention, recrystallization, slurry, and compression, and analyzed using said DSC method, a single endotherm occurring at a temperature range from about 155° C. to about 160° C., and more preferably from about 157° C. to about 159° C., confirms the presence of Form A of fluoxetine hydrochloride (FIGS. **6** and **8** for the compression and slurry methods, respectively). Interestingly, when such DSC method was used to analyze Form A prepared via such recrystallization method and placed under accelerated stability conditions (40° C. and 75% relative humidity) for less than one week, the presence of Form A was confirmed, but two additional polymorphs of fluoxetine hydrochloride, Forms D and E, were prepared (FIG. **11**). Accordingly, the slurry method for preparing pure and essentially pure Form A is preferred, while the compression method is especially preferred.

For additional confirmation of the presence of Form of fluoxetine hydrochloride in pure form, single x-ray crystallography, x-ray powder diffraction, and differential scanning calorimetry can be used together.

Furthermore, x-ray powder diffraction and differential scanning calorimetry can be used to identify essentially pure Form A. The powder pattern for essentially pure Form A is consistent with those for fluoxetine hydrochloride API and pure Form A as taught herein. However, essentially pure

Form A is further characterized by having at least two endotherms as determined by DSC run at a maximum rate of 1° C. per minute. Essentially pure Form A is defined by an increase in Form A and decrease of other polymorphs of fluoxetine hydrochloride compared to the starting material when prepared, for example, as taught herein, but the crystallization process is not permitted to run to completion which would form pure Form A. However, it is preferred that the amount of fluoxetine hydrochloride polymorphs other than Form A does not exceed an amount greater than about ten percent (w/w) and, more preferably, does not exceed an amount greater than about five percent (w/w).

For the purpose of this invention, the term "pure" refers to Form A of fluoxetine hydrochloride being in a concentration such that other fluoxetine polymorphs are present in amounts generally below limits detectable by conventional technology, particularly the Differential Scanning Calorimetry (DSC) method taught in Example 12 herein. Although the present invention provides for pure and essentially pure Form A of fluoxetine hydrochloride, it is particularly preferred, of course, to eliminate all of the other polymorphic impurities to provide pure Form A of the present invention.

Fluoxetine hydrochloride API can be prepared by a multitude of processes known in the art (see e.g., U.S. Pat. Nos. 4,314,081; 5,166,437; and 5,225,585). The compositions of the present invention are preferably prepared by using such fluoxetine hydrochloride API as the starting material. The recrystallization and slurry methods set forth below can be used as the final steps in many crystallization processes in situ for the preparation of fluoxetine hydrochloride, without requiring a "recrystallization" processes, resulting in the preparation of Form A, preferably in pure and essentially pure form. Preferred methods for the preparation of Form A are set forth below, but are not intended to limit the scope of the present invention.

Preparation of Form A

I. Recrystallization Method

Fluoxetine hydrochloride API is recrystallized (or crystallized in situ, as the case may be) into Form A by dissolving such API in a suitable solvent in excess. Suitable solvents are those which are capable of dissolving fluoxetine hydrochloride so that a solution is formed, and include solvents across various classes including, for example, protic, aprotic, polar, and non-polar. Alcohol-based solvents are preferred and methanol is especially preferred. The resulting solution is filtered and permitted to recrystallize, most preferably at a fixed temperature, by evaporation. The temperature used for the evaporation step should be held constant at a temperature which permits the recrystallization of the starting material to Form A. A temperature range from about 0° C. to about 60° C. is preferred, while a temperature range from about 15° C. to about 40° C. is more preferred, and about ambient temperature is most preferred. This method has provided pure and essentially pure Form A of fluoxetine hydrochloride depending upon whether this recrystallization process is allowed to run to completion. However, this method is the least preferred of the methods taught herein. This method typically produces Form A, which, due to the method used, may transform to at least two more previously unidentified polymorphic forms of fluoxetine hydrochloride, designated as Forms D and E.

II. Slurry Method

Fluoxetine hydrochloride API is recrystallized (or crystallized in situ, as the case may be) into stable Form A by adding such API to a suitable solvent until a slurry is formed. Suitable solvents are those which are capable of sufficiently dissolving such API to form a slurry and establish a dynamic solubility equilibrium. Alcohol-based solvents are preferred and methanol is especially preferred. The resulting slurry is stirred until Form A is in pure or essentially pure form, as desired. Typically, the slurry is stirred for about two days depending upon batch size and solvent used, preferably at ambient temperature, and filtered. Most preferably, this process is run at a fixed temperature. For the preparation of pure Form A, it is preferred to allow this process to run to completion, as demonstrated by the preferred DSC method taught herein. Acceptable temperature ranges are those which will permit the transformation of the starting material to Form A, while a temperature range from about 0° C. to about 60° C. is preferred, a temperature range from about 15° C. to about 40° C. is more preferred, and about ambient temperature is most preferred.

III. Compression Method

Particularly surprising was the discovery that Form A of fluoxetine hydrochloride can be prepared via compression. Various pieces of equipment may be used during the preparation of pharmaceutical products to provide a pressure of about 100 pounds per square inch (psi) to about 5000 psi, or greater. Such equipment includes, for example, hydraulic presses. Such equipment can provide sufficient pressure to convert the existing multiple polymorphic forms of fluoxetine hydrochloride to stable, pure or essentially pure Form A by regulating the amount of pressure used in this method. Preferably, at least about 100 psi is used. It is also preferred to use sufficient pressure without changing the other physical properties of Form A which are reasonably necessary for preparation of the respective drug product. Confirmation of the relative purity of Form A prepared by this process is also confirmed using DSC.

Accordingly, the present invention provides, in part, pure and essentially pure Form A of fluoxetine hydrochloride, and methods for the preparation thereof. The present invention further provides methods for reducing, minimizing, and eliminating polymorphic contaminants (i.e., fluoxetine hydrochloride Forms B and C), and inhibiting the formation of other polymorphic forms of fluoxetine hydrochloride (i.e., Forms D and E).

It was also unexpectedly discovered that amorphous fluoxetine hydrochloride can be used as an intermediate for the preparation of Form A of the present invention. The starting material for this process, generally, is fluoxetine hydrochloride. Such starting material is heated to above the melting point thereof, then slowly cooled to about ambient temperature. It is preferred to heat such starting material to just beyond the melting point thereof (generally, just beyond about 155° C. to about 160° C.) to avoid over heating such starting material to the point that it decomposes in part or in whole. The sample initially remains in the amorphous state, as confirmed by x-ray powder diffraction, but recrystallized into Form A following nucleation. Nucleation can actively be induced (i.e., physically disturbing the sample) or passively induced by the use of natural forces by permitting the sample to be exposed to nucleation forces including, for example, dust particles, vibration, or air currents.

Accordingly, the present invention further provides amorphous fluoxetine hydrochloride, generally useful as an intermediate for the preparation of Form A of the present invention, and methods for preparing such Form A therefrom.

The present invention further provides methods of using Form A of fluoxetine hydrochloride, preferably in pure and essentially pure form, for inhibiting serotonin uptake in

mammals comprising administering to a mammal requiring increased neurotransmission of serotonin an effective amount of one or more desired form(s) of fluoxetine hydrochloride of the present invention. Pure Form A is preferred. Disease states requiring such inhibition of serotonin uptake include, for example, depression, anxiety, alcoholism, chronic pain, eating disorders such as, for example, obesity and bulimia, and smoking cessation.

For the most effective administration of novel Form A of the present invention, it is preferred to prepare a pharmaceutical formulation preferably in unit dose form, comprising one or more of the active ingredients of the present invention and one or more pharmaceutically acceptable carrier, diluent, or excipient. As used herein, the term "active ingredient" refers to any of the embodiments set forth herein, particularly Form A of fluoxetine hydrochloride in pure or essentially pure form.

Such pharmaceutical formulation may, without being limited by the teachings set forth herein, include a solid form of the present invention which is blended with at least one pharmaceutically acceptable excipient, diluted by an excipient or enclosed within such a carrier that can be in the form of a capsule, sachet, tablet, buccal, lozenge, paper, or other container. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient(s). Thus, the formulations can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, capsules (such as, for example, soft and hard gelatin capsules), suppositories, sterile injectable solutions, and sterile packaged powders.

Examples of suitable excipients include, but are not limited to, starches, gum arabic, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as, for example, talc, magnesium stearate and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propyl- hydroxybenzoates; sweetening agents; or flavoring agents. Polyols, buffers, and inert fillers may also be used. Examples of polyols include, but are not limited to: mannitol, sorbitol, xylitol, sucrose, maltose, glucose, lactose, dextrose, and the like. Suitable buffers encompass, but are not limited to, phosphate, citrate, tartrate, succinate, and the like. Other inert fillers which may be used encompass those which are known in the art and are useful in the manufacture of various dosage forms. If desired, the solid pharmaceutical compositions may include other components such as bulking agents and/or granulating agents, and the like. The compositions of the invention can be formulated so as to provide quick, sustained, controlled, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

In certain embodiments of the invention, the active ingredient(s) may be made into the form of dosage units for oral administration. The active ingredient(s) may be mixed with a solid, pulverant carrier such as, for example, lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an antifriction agent such as for example, magnesium stearate, calcium stearate, and polyethylene glycol waxes. The mixture is then pressed into tablets or filled into capsules. If coated tablets, capsules, or pulvules are desired, such tablets, capsules, or pulvules may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide, or with a lacquer dissolved in the volatile organic solvent or mixture of solvents. To this coating, various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared in which capsules contain a mixture of the active ingredient(s) and vegetable oil or non-aqueous, water miscible materials such as, for example, polyethylene glycol and the like. Hard gelatin capsules may contain granules or powder of the active ingredient in combination with a solid, pulverulent carrier, such as, for example, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Tablets for oral use are typically prepared in the following manner, although other techniques may be employed. The solid substances are gently ground or sieved to a desired particle size, and a binding agent is homogenized and suspended in a suitable solvent. The active ingredient(s) and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension. The moistening typically causes the particles to aggregate slightly, and the resulting mass is gently pressed through a stainless steel sieve having a desired size. The layers of the mixture are then dried in controlled drying units for a pre-determined length of time to achieve a desired particle size and consistency. The granules of the dried mixture are gently sieved to remove any powder. To this mixture, disintegrating, anti-friction, and anti-adhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size.

In the event that the above formulations are to be used for parenteral administration, such a formulation typically comprises sterile, aqueous and non-aqueous injection solutions comprising one or more active ingredients for which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats, and solute; which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous suspensions may include suspending agents and thickening agents. The formulations may be present in unit-dose or multi-dose containers, for example, sealed ampules and vials. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

Liquid preparations for oral administration are prepared in the form of solutions, syrups, or suspensions with the latter two forms containing, for example, active ingredient(s), sugar, and a mixture of ethanol, water, glycerol, and propylene glycol. If desired, such liquid preparations contain coloring agents, flavoring agents, and saccharin. Thickening agents such as carboxymethylcellulose may also be used.

As such, the pharmaceutical formulations of the present invention are preferably prepared in a unit dosage form, each dosage unit containing from about 5 mg to about 200 mg, more usually from about 10 mg to about 40 mg of the active ingredient(s). In liquid form, dosage unit contains from about 5 to about 200 mg, more usually about 10 mg to about 40 mg of active ingredient(s). The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects/patients or other mammals, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with preferably, at least one pharmaceutically acceptable carrier, diluent, or excipient.

The following examples are illustrative and are not intended to limit the scope of the invention in any way.

Formulation 1
Hard gelatin 20 mg capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
active ingredient ethanedioate	20
starch, dried	200
magnesium stearate	10
Total	230

The above ingredients are mixed and filled into hard gelatin capsules in 230 mg quantities.

Formulation 2
A 20 mg tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
active ingredient	20
cellulose, microcrystalline	400
silicon dioxide, fumed	10
stearic acid	5
Total	435

The components are blended and compressed to form tablets each weighing 435 mg.

Formulation 3

Tablets each containing 20 mg of active ingredient are made as follows:

active ingredient	20 mg
starch	45 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone (as 10% solution in water)	4 mg
sodium carboxymethyl starch	4.5 mg
magnesium stearate	0.5 mg
talc	1 mg
Total	110 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly, the solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50 ° C. and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 110 mg.

Formulation 4
Capsules each containing 10 mg of medicament are made as follows:

active ingredient	10 mg
starch	59 mg
microcrystalline cellulose	59 mg
magnesium stearate	2 mg
Total	130 mg

-continued

Formulation 4
Capsules each containing 10 mg of medicament are made as follows:

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 130 mg quantities.

Formulation 5

Suspensions each containing 20 mg of medicament per 5 ml dose are made as follows:

active ingredient	20 mg
sodium carboxymethyl cellulose	50 mg
syrup	1.25 ml
benzoic acid solution	0.10 ml
flavor	q.v.
color	q.v.
purified water to total	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 6

An intravenous formulation may be prepared as follows:

active ingredient	100 mg
isotonic saline	1000 ml

The solution of the above ingredients is administered intravenously at a rate of 1 ml per minute to a subject suffering from depression

The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the present invention.

EXAMPLE 1

Form A Via the Recrystallization Method

To a 20 mL beaker containing 10 mL of methanol was added an amount of fluoxetine hydrochloride API such that the resulting suspension was at or near the saturation point. The suspension was then magnetically stirred for about 15 minutes and filtered through a 0.45 μm polytrifluoroethylene ("PTFE") filter. The resulting solution was allowed to stand undisturbed at ambient temperature until the solvent evaporated (about 1 to 2 days). X-ray powder diffraction (XRD) confirmed the end product is fluoxetine hydrochloride, and differential scanning calorimetry (DSC) confirmed the presence of pure Form A polymorph of fluoxetine hydrochloride.

EXAMPLE 2

Form A Via the Recrystallization Method

The process set forth in Example 1 above was used, but water rather than methanol was used as a solvent. XRD confirmed the end product is fluoxetine hydrochloride, and DSC confirmed the presence of pure Form A polymorph of fluoxetine hydrochloride.

EXAMPLE 3

Form A Via the Recrystallization Method

The process set forth in Example 1 above was used, but dimethylformamide rather than methanol was used as a solvent. XRD confirmed the end product is fluoxetine

hydrochloride, and DSC confirmed the presence of pure Form A polymorph of fluoxetine hydrochloride.

EXAMPLE 4

Form A Via the Slurry Method

To a 20 mL beaker containing 10 mL of methanol was added sufficient fluoxetine hydrochloride API, in excess, to form a slurry. The resulting slurry was magnetically stirred for about 48 hours at ambient temperature. The slurry was filtered (using a 0.45 μm PTFE filter) and the collected solid material was dried under a vacuum at ambient temperature for about 4 hours. XRD confirmed the end product is fluoxetine hydrochloride, and DSC confirmed the presence of pure Form A polymorph of fluoxetine hydrochloride.

EXAMPLE 5

Form A Via the Compression Method

A 100 mg sample of fluoxetine hydrochloride API was placed in a dye and compressed by a Carver Press (Fred S. Carver, Inc.; Menomonee Falls, Wis.) at about 100 psi to obtain a pellet. The pellet was broken apart using a scalpel and tested. XRD confirmed the end product is fluoxetine hydrochloride, and DSC confirmed the presence of pure Form A polymorph of fluoxetine hydrochloride.

EXAMPLES 6-9

Form A Via the Compression Method

Using the procedure set forth in Example 5 above, fluoxetine hydrochloride API samples were compressed at 1000, 2000, 4000, and 4500 psi. XRD confirmed that each sample is fluoxetine hydrochloride, and DSC confirmed the presence of pure Form A polymorph of fluoxetine hydrochloride.

EXAMPLE 10

Form A Via Amorphous Fluoxetine Hydrochloride

A sample of 50 mg of fluoxetine hydrochloride API was heated by hot stage microscopy to 170° C. until the entire sample entered the "glass" phase. The sample was allowed to cool at ambient temperature. XRD confirmed the resulting fluoxetine hydrochloride is in amorphous form, and no melting point was observed using DSC. Following nucleation, XRD and DSC confirmed that the resulting material is crystalline fluoxetine hydrochloride as Form A thereof.

EXAMPLE 11

Differential Scanning Calorimetry for Fluoxetine Hydrochloride

A sample of about 10 mg was placed in a sealed aluminum sample holder and was heated from 30° C. to 180° C., at 10° C. per minute under a 40 mL per minute nitrogen purge, using a Mettler-Toledo (Columbus, Ohio) DSC821^e differential scanning calorimeter with Star^e software package (also from Mettler-Toledo). Endotherms demonstrated the presence of at least two polymorphs in fluoxetine hydrochloride API, designated Forms A and B of fluoxetine hydrochloride API. However, the resolution was less than desired, and the method set forth in Example 12 herein was developed as a required method.

EXAMPLE 12

Differential Scanning Calorimetry for Fluoxetine Hydrochloride

The method described in Example 11 was used, except the heating rate was changed from 10° C. per minute to a heating rate of 1° C. per minute from 145° C. to 175° C. The improved resolution from use of this method resulted in the observation of at least three polymorphs of fluoxetine hydrochloride API, designated Forms A, B, and C fluoxetine hydrochloride API.

EXAMPLE 13

Differential Scanning Calorimetry for Pure Form A of Fluoxetine Hydrochloride

The method used in Example 12 was used, except the fluoxetine hydrochloride from Examples 2 and 3 were tested rather than fluoxetine hydrochloride API. A single endotherm from about 155° C. to about 160° C. confirmed the presence of a single fluoxetine hydrochloride polymorph, identified as pure Form A via the method taught in Example 14.

EXAMPLE 14

Determination of the Single Crystal Structure of Form A of Fluoxetine Hydrochloride

Single Crystal X-Ray Diffraction was used to determine the single crystal structure of Form A of fluoxetine hydrochloride. Without being bound to theory, it is believed that a crystalline material diffracts X-rays due to the constructive and destructive interference of the scattering of X-rays from the atoms of the molecule within the crystal lattice. The intensity and positions of the diffraction spots produced by the crystal is capable of generating structural information about the locations of the atoms in the molecule of a crystal.

In this instance, a single crystal of the material to be examined is mounted at the end of a glass fiber. The crystal is aligned in the diffractometer in a specific orientation. The diffraction spots are measured, then the crystal is rotated to the next position. The above sequence is then repeated until thousands of individual diffraction spots are measured and recorded. The diffraction spots are then analyzed and the data phased to generate an electron density map from which a molecular structure of the molecule is uniquely determined. The X-ray diffraction data is generated using either a Nonius CAD4 diffractometer or a Nonius Kappa CCD diffractometer made commercially available by Nonius Corporation of Delft, Netherlands. Pure Form A of fluoxetine hydrochloride prepared in the methods taught herein is characterized by the following single crystallization parameters:

crystal class	orthorhombic
space groups	Pbca (#61)
a(Å)	10.3754 (4)
b(Å)	10.4603 (2)
c(Å)	32.3412(12)
V(Å^3)	3510.0(3)
d calc (g/cm^3)	1.31
R, R_w	0.038, 0.038

EXAMPLE 15

X-ray Powder Diffraction for Fluoxetine Hydrochloride

A sample of about 50 mg of fluoxetine hydrochloride was placed on a zero-background sample plate and analyzed using copper Kα Radiation (λ=1.5418 Å) from 2 to 40 degrees in 2-theta at 2.4 degrees per minute. A Siemens D500 automated diffractometer (Munich, Germany) with MDI software (Livermore, Calif.) was used for the analysis and processing of the data.

What is claimed is:

1. A pharmaceutical formulation comprising Form A of fluoxetine hydrochloride in pure form and at least one pharmaceutically acceptable carrier, diluent, or excipient.

2. A pharmaceutical formulation comprising Form A of fluoxetine hydrochloride in pure form characterized by having an x-ray powder diffraction pattern consistent with fluoxetine hydrochloride, and further characterized by having a single endotherm as determined by differential scanning calorimetry run at a maximum rate of 1° C. per minute, as an active ingredient, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

3. A pharmaceutical formulation according to claim 2 wherein said single DSC endotherm occurs in the temperature range from about 155° C. to about 160° C.

4. A pharmaceutical formulation according to claim 2 wherein said single DSC endotherm occurs in the temperature range from about 157° C. to about 159° C.

5. A pharmaceutical formulation comprising Form A of fluoxetine hydrochloride in pure form characterized by the following single crystallographic parameters:

crystal class	orthorhombic
space groups	Pbca (#61)
a(Å)	10.3754 (4)
b(Å)	10.4603 (2)
c(Å)	32.3412(12)
V(Å^3)	3510.0(3)
d calc (g/cm^3)	1.31
R, R_w	0.038, 0.038

as an active ingredient, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

6. A pharmaceutical formulation according to claim 5 wherein said Form A of fluoxetine hydrochloride is further characterized by an x-ray powder diffraction pattern consistent with fluoxetine hydrochloride, and further characterized by having a single endotherm as determined by differential scanning calorimetry run at a maximum rate of 1° C. per minute, as an active ingredient, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

7. A pharmaceutical formulation according to claim 6 wherein said single DSC endotherm occurs in the temperature range from about 155° C. and 160° C.

8. A pharmaceutical formulation according to claim 6 wherein said single DSC endotherm occurs in the temperature range from about 157° C. and 159° C.

9. A pharmaceutical formulation comprising Form A of fluoxetine hydrochloride in essentially pure form and at least one pharmaceutically acceptable carrier, diluent or excipient.

10. A pharmaceutical formulation comprising Form A of fluoxetine hydrochloride characterized by having an x-ray diffraction pattern consistent with fluoxetine hydrochloride, and further characterized by having at least two endotherms as determined by differential scanning calorimetry run at a maximum rate of 1° C. per minute as an active ingredient, provided that the amount of fluoxetine hydrochloride polymorphs other than Form A does not exceed an amount greater than about ten percent (w/w), and at least one pharmaceutically acceptable carrier, diluent, or excipient.

11. A pharmaceutical formulation according to claim 10 wherein the peak of said DSC endotherms occurs in the temperature range from about 155° C. to about 160° C.

12. A pharmaceutical formulation according to claim 10 wherein said Form A is further characterized by the following crystallographic parameters:

crystal class	orthorhombic
space groups	Pbca (#61)
a(Å)	10.3754 (4)
b(Å)	10.4603 (2)
c(Å)	32.3412(12)
V(Å^3)	3510.0(3)
d calc (g/cm^3)	1.31
R, R_w	0.038, 0.038

13. A pharmaceutical formulation according to claim 12 wherein the peak of said DSC endotherms occurs in the temperature range from about 155° C. to about 160° C.

14. A pharmaceutical formulation comprising Form A of fluoxetine hydrochloride characterized by having an x-ray diffraction pattern consistent with fluoxetine hydrochloride, and further characterized by having at least two endotherms as determined by differential scanning calorimetry run at a maximum rate of 1° C. per minute as an active ingredient, provided that the amount of fluoxetine hydrochloride polymorphs other than Form A does not exceed an amount greater than about five percent (w/w), and at least one pharmaceutically acceptable carrier, diluent, or excipient.

15. A pharmaceutical formulation according to claim 14 wherein the peak of said DSC endotherms occurs in the temperate range from about 155° C. to about 160° C.

16. A pharmaceutical formulation according to claim 14 wherein said Form A is further characterized by the following crystallographic parameters:

crystal class	orthorhombic
space groups	Pbca (#61)
a(Å)	10.3754 (4)
b(Å)	10.4603 (2)
c(Å)	32.3412(12)
V(Å^3)	3510.0(3)
d calc (g/cm^3)	1.31
R, R_w	0.038, 0.038

17. A pharmaceutical formulation according to claim 16 wherein the peak of said DSC endotherms occurs in the temperature range from about 155° C. to about 160° C.

18. A pharmaceutical formulation according to any one of claims 1 through 17 wherein said fluoxetine hydrochloride is the sole active ingredient.

19. A method for inhibiting serotonin uptake in mammals comprising administering to a mammal requiring increased neurotransmission of serotonin an effective amount of a pharmaceutical formulation as claimed in any one of claims 1 through 17.

20. A method according to claim 19 wherein said fluoxetine hydrochloride is the sole active ingredient.

* * * * *

EXHIBIT "2"

Hale and Dorr LLP
1455 Pennsylvania Avenue N.W. 10th Floor
Washington, D.C. 20004
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Fax: (202) 942-8484

fax transmittal

to:	David Cade Acting General Counsel Office of General Counsel Department of Health and Human Services	(202) 690-7998
	Michael Landa Acting General Counsel Office of the Chief Counsel Food and Drug Administration	(301) 827-3054
from:	Louise Howe	
date:	August 1, 2001	
pages:	2	

Client Matter Number:
Transmitted By:

EXHIBIT "2"

FOLEY & LARDNER

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EMAIL ADDRESS
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CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA DHL

John Maxwell Shaw Montgomery
CEO
ALPHAPHARM LTD.
Chase Building 2
Wentworth Park Road
Glebe NSW 2037
Australia

Re: U.S. Patent No. 6,258,853

Dear Mr. Montgomery:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Alphapharm's generic Prozac® product. Accordingly, we bring the '853 patent to your attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Alphapharm's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Alphapharm as they issue.

We ask for Alphapharm's prompt response to this letter. We will follow up in a week's time, unless we hear from Alphapharm earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

TECHNICAL INFORMATION ON ALPHAPHARM'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Alphapharm.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Alphapharm's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Alphapharm or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA FEDERAL EXPRESS

Paul M. Bisaro
President and COO
BARR LABORATORIES, INC.
300 Corporate Drive
Blauvelt, NY 10913

Re: U.S. Patent No. 6,258,853

Dear Mr. Bisaro:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Barr's generic Prozac® product. Accordingly, we bring the '853 patent to Barr's attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Barr's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Barr as they issue.

We ask for Barr's prompt response to this letter. We will follow up in a week's time, unless we hear from Barr earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

2.610638.1

TECHNICAL INFORMATION ON BARR'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Barr.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Barr's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Barr or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA DHL

Dr. Bernhard Scheuble
Chairman
MERCK KGaA
Frankfurter Str. 250
64293 Darmstadt
Germany

Re: U.S. Patent No. 6,258,853

Dear Dr. Scheuble:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Merck KGaA's generic Prozac® product. Accordingly, we bring the '853 patent to your attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Merck KGaA's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Merck KGaA as they issue.

We ask for Merck KGaA's prompt response to this letter. We will follow up in a week's time, unless we hear from Merck KGaA earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

TECHNICAL INFORMATION ON MERCK KGaA'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Merck KGaA.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Merck KGaA's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Merck KGaA or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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CLIENT/MATTER NUMBER
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July 18, 2001

VIA FEDERAL EXPRESS

David M. Hurley
President and CEO
GENEVA PHARMACEUTICALS
2555 W. Midway Blvd.
Broomfield, CO 80020

Re: U.S. Patent No. 6,258,853

Dear Mr. Hurley:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Geneva Pharmaceuticals' generic Prozac® product. Accordingly, we bring the '853 patent to Geneva's attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Geneva's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Geneva as they issue.

We ask for Geneva's prompt response to this letter. We will follow up in a week's time, unless we hear from Geneva earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

12.510791.1

TECHNICAL INFORMATION ON GENEVA'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Geneva.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Geneva's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Geneva or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA FEDERAL EXPRESS

Kenneth I. Sawyer
President and CEO
PAR PHARMACEUTICAL, INC.
One Ram Ridge Rd.
Spring Valley, NY 10977

Re: U.S. Patent No. 6,258,853

Dear Mr. Sawyer:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Par Pharmaceutical's generic Prozac® product. Accordingly, we bring the '853 patent to Par Pharmaceutical's attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Par Pharmaceutical's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Par Pharmaceutical as they issue.

We ask for Par Pharmaceutical's prompt response to this letter. We will follow up in a week's time, unless we hear from Par Pharmaceutical earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

12.611078.1

TECHNICAL INFORMATION ON PAR PHARMACEUTICAL'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Par Pharmaceutical.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Par Pharmaceutical's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Par Pharmaceutical or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA FEDERAL EXPRESS

Kenneth I. Sawyer
President and CEO
PHARMACEUTICAL RESOURCES, INC.
One Ram Ridge Rd.
Spring Valley, NY 10977

Re: U.S. Patent No. 6,258,853

Dear Mr. Sawyer:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Pharmaceutical Resources, Inc.'s (PRI) generic Prozac® product. Accordingly, we bring the '853 patent to PRI's attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers PRI's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to PRI as they issue.

We ask for PRI's prompt response to this letter. We will follow up in a week's time, unless we hear from PRI earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

TECHNICAL INFORMATION ON PRI'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to PRI.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate PRI's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by PRI or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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WRITER'S DIRECT LINE
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EMAIL ADDRESS
mkaminski@foleylaw.com

CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA FEDERAL EXPRESS

Paul Campanelli
Vice President
REDDY-CHEMINOR, INC. USA
66 South Maple Ave.
Ridgewood, NJ 07450

Re: U.S. Patent No. 6,258,853

Dear Mr. Campanelli:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Reddy-Cheminor's generic Prozac® product. Accordingly, we bring the '853 patent to your attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Reddy-Cheminor's product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Reddy-Cheminor as they issue.

We ask for Reddy-Cheminor's prompt response to this letter. We will follow up in a week's time, unless we hear from Reddy-Cheminor earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

2.611053.1

TECHNICAL INFORMATION ON REDDY-CHEMINOR'S GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Reddy-Cheminor.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Reddy-Cheminor's generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

C. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to pressure. The amount and duration of the applied pressure should be stated.

3. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API used to prepare your Drug Product immediately following its synthesis.

4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Reddy-Cheminor or the manufacturer for use in your Drug Product.

FOLEY & LARDNER

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CLIENT/MATTER NUMBER
046121/0105

July 18, 2001

VIA DHL

Dr. Anji Reddy
Chairman
DR. REDDY'S LABORATORIES
7-1-27 Ameerpet
Hyderabad 500 016
India

Re: U.S. Patent No. 6,258,853

Dear Dr. Reddy:

We represent aaiPharma Inc. aaiPharma owns U.S. Patent No. 6,258,853, a copy of which is enclosed.

Based on our best efforts to investigate the situation, we believe the '853 patent may cover Dr. Reddy's Laboratories' generic Prozac® product. Accordingly, we bring the '853 patent to your attention.

However, by the attachment to this letter, we are asking for certain information that will allow us to resolve more definitively whether the '853 patent covers Dr. Reddy's Laboratories' product. This information includes samples of the Active Pharmaceutical Ingredient ("API") (fluoxetine HCl), a description of the process steps carried out during and after preparation of the API, and an identification of your API supplier(s).

Further, aaiPharma also expects a number of related patents to issue over the next months. We will forward these to Dr. Reddy's Laboratories as they issue.

We ask for Dr. Reddy's Laboratories' prompt response to this letter. We will follow up in a week's time, unless we hear from Dr. Reddy's Laboratories earlier.

Sincerely,

Michael D. Kaminski

Michael D. Kaminski

Attachment
Enclosures

cc: Steven A. Fontana
Beth A. Burrous

12.610705.1

TECHNICAL INFORMATION ON DR. REDDY'S LABORATORIES' GENERIC PROZAC® PRODUCT

1. A detailed description of the process used to prepare and process the fluoxetine hydrochloride ("HCl") API.

   A. The description should identify the supplier or suppliers of the fluoxetine HCl API to Dr. Reddy's Laboratories.

   B. The description should identify each step used to synthesize the fluoxetine HCl API.

   C. The description should identify each step, whether chemical or physical, used to purify the fluoxetine HCl API.

   D. The description should identify any step used to physically treat the fluoxetine HCl API prior to shipping.

   E. The description should identify the specifications used to assess the quality of the fluoxetine HCl API before shipping and also for release of such API for use in the preparation drug product, including any particle size specifications.

   F. The description should identify any other processing steps involving the fluoxetine HCl API before shipping.

2. A detailed description of the process used to formulate Dr. Reddy's Laboratories' generic fluoxetine HCl drug product as tentatively approved by the FDA (the "Drug Product").

   A. The description should identify each solvent, wetting agent, excipient, or other substance that is mixed or otherwise comes in contact with the fluoxetine HCl API during preparation of your Drug Product.

   B. The description should specifically identify any step in the formulation process which exposes the fluoxetine HCl API (whether in pure form or mixed with one or more excipients) to one or more solvents or other liquids. The identity and amount of such liquids should be stated. As used herein, the term "excipient" refers to, without limitation, any one or more carrier, diluent, solvent, wetting agent, plasticizing agent, and the like used in the preparation of your Drug Product.

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4. Please immediately ship to us, for each of five different lots of fluoxetine HCl API: Samples (1 gram each) of such API as released by Dr. Reddy's Laboratories or the manufacturer for use in your Drug Product.

EXHIBIT "3"

aaiPharma™
DEVELOPING CHEMISTRY INTO MEDICINE

2320 Scientific Park Drive
Wilmington, N.C. 28405

Phone: 1.910.254.7000
Fax: 1.910.815.2340
1.800.575.4224

Via Federal Express

July 18, 2001

Ms. Mary A. Holovac
Division of Data Management Services (HFD-90)
Center for Drug Evaluation and Research
Food and Drug Administration
12400 Parklawn Drive, Room 3012
Rockville, Maryland 20857

RE: Fluoxetine Hydrochloride
US Patent No. 6,258,853

Dear Ms. Holovac:

I am writing in accordance with 21 C.F.R. 314.53(f) to advise the Agency that an NDA applicant has failed to submit required patent information under 21 U.S.C. 355(c)(2). U.S. Pat. No. 6,258,853 (the "'853 patent", copy attached) was issued on July 10, 2001 on one form of the active ingredient in fluoxetine hydrochloride, which is currently marketed by Eli Lilly & Company (Lilly) as, among other trade names, Prozac® pursuant to NDA 18-936. The '853 patent claims the drug product and a method of using the drug product for which the Prozac® NDA was submitted, and is one with respect to which a claim of patent infringement could reasonably be asserted. Therefore, under the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. 355(c)(2), Lilly is legally obligated to submit the patent for listing in the Orange Book.

Lilly has informed aaiPharma that it does not plan to submit this patent for listing in the Orange Book. After reviewing the legal requirements, aaiPharma has concluded that Lilly must list the '853 patent in the Orange Book. The Act provides a two-part test for determining whether a patent must be submitted for inclusion in the Orange Book. A brief review of the requirements follows.

The first requirement for patent listing in the Orange Book is that a patent must claim the drug, or a method of using the drug, for which the applicant submitted the NDA. The '853 patent claims, among other things, one form of the active ingredient of fluoxetine hydrochloride. Research by aaiPharma leading to issuance of the '853 patent shows that fluoxetine hydrochloride as manufactured by Lilly consists of multiple forms. The '853 patent claims a pharmaceutical substance comprising, among other things, Form A of fluoxetine hydrochloride (either alone or with as much as 10% of the other forms of fluoxetine hydrochloride), and a method of using this substance. Therefore, the '853 patent claims the drug, and a method of using the drug, for which the Prozac® NDA was submitted.

The second requirement for patent listing is that a claim of patent infringement could reasonably be asserted. Qualified patent counsel has reviewed the '853 patent and concluded that a claim of patent infringement may reasonably be asserted. Based on the foregoing, the '853 patent meets both requirements for patent listing, and, therefore, section 355(c)(2) requires Lilly to list the patent within 30 days of July 10, 2001.

The purpose of the Hatch-Waxman patent listing provisions is to protect the rights of the patent owner consistent with the public interest in marketing lower cost generic drugs. The Orange Book patent listing requirements enable the patent owner, through statutorily required action of the NDA applicant, to give public notice that a patent has issued that may affect an ANDA applicant's ability to market a generic drug. In this instance, a private party, Lilly, who does not have an interest in the '853 patent, is frustrating the intent of the law to protect a patent holder's rights. The following language appears in the preamble to the final ANDA rule, in response to a comment that only an NDA applicant would be injured by the failure to list a patent:

> "The agency disagrees with the assertion that the NDA applicant would be the only party injured by the failure to list a patent. The patent holder may be injured if the patented invention is made, sold, or used without the patent holder's knowledge or consent."

59 Federal Register 50338, 50344 (October 3, 1994). It is imperative that FDA not permit Lilly to compromise aaiPharma's ownership rights in the '853 patent under Hatch-Waxman.

From a regulatory and scientific standpoint, it is important that the '853 patent be listed for consideration by FDA and the ANDA applicants. aaiPharma has discovered that solid state fluoxetine hydrochloride exhibits polymorphism through the existence of multiple forms of fluoxetine hydrochloride, and subsequently obtained the '853 patent. In addition, processes that minimize the extent and availability of fluoxetine hydrochloride forms other than Form A and,

more importantly, provide pure Form A, have also been developed by aaiPharma. We further note, incidentally, that the polymorphic structure of drug substances is considered relevant in many contexts. In fact, FDA has recognized the need to investigate polymorphism in drug substances and drug products, and where appropriate, to set acceptance criteria. See, e.g., FDA's ICH Guidelines on polymorphism at 65 Fed. Reg. 83041 (December 29, 2000).

aaiPharma respectfully requests that FDA contact Lilly to confirm the correctness of Lilly's omission of information about the '853 patent from the list of Prozac®-related patents in the Orange Book. Irrespective of Lilly's response, aaiPharma believes that FDA has an obligation to effect the Congressional intent of protecting patent owner rights whether or not the patent owner or licensee is an NDA applicant.

Sincerely,

Vivian Madison Pratt
Sr. Vice President, Regulatory Affairs
aaiPharma, Inc.

VMP:bjj

Attachment: US Patent No. 6,258,853

July 24, 2001

Lilly Research Labs
Lilly Corporate Center
307 East McCarty St.
Indianapolis, IN 46285

Dear NDA Applicant:

The Food and Drug Administration (FDA) has received the enclosed challenge to the patent information for your new drug application (NDA) 18-936 for Prozac (Fluoxetine Hydrochloride).

Under the procedures established by 21 CFR 314.53(f), persons disputing the accuracy or relevance of patent information submitted to the agency are requested to notify the agency in writing stating the grounds for disagreement. The agency then will request the applicable NDA holder to confirm the correctness of the patent information submitted. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).

Therefore, FDA requests that you review the enclosed challenge and, as soon as possible, provide FDA with written confirmation that the challenged patent information for NDA 18-936 is correct. Please submit any corrections that need to be made to the patent and exclusivity information addendum of the Orange Book. Changes must be submitted to the address below.

Please be advised that, as described at 21 CFR 314.53(d), for a new patent to be considered timely-filed, it must be submitted to FDA within 30 days of the date the Patent and Trademark Office issued the patent.

Sincerely,

Mary Ann Holovac, R.Ph.
Information Services Team

Mailing address: (US Mail)
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services